

Remarks

Applicant respectfully requests reconsideration. Claims 1-13, 18, 23, 28, 33, 40, 47, and 49 were previously pending and under consideration. By this Amendment Applicant currently amends claims 13, 18, 23, 28, 33, 40, 47, and 48. No claims are canceled. No new claims are presented. As a result, claims 1-13, 18, 23, 28, 33, 40, 47, and 49 are currently pending and under consideration. No new matter has been added.

In accord with the Examiner's comments on page 2 of the Office Action, Applicant has currently amended claims 13, 18, 23, 28, 33, and 40, replacing "a" with "the" prior to "fusion protein," to clarify that these claims embrace each and every fusion protein of the claims from which they depend.

Also in accord with the Examiner's comments on page 2 of the Office Action, Applicant has currently amended claims 47 and 48, replacing "a" with "the" prior to the second instance of "subject," to provide a nexus between the "subject" and its precedent in the preamble.

Applicant confirms that the information disclosure statement filed on 10/8/04 did not include a form 1449. The information disclosure statement filed on 10/8/04 included an International Preliminary Examination Report.

Applicant acknowledges that the Examiner indicated that the drawings are acceptable for examination.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1, 2, 5 and 7-12 under 35 U.S.C. §103(a) as being unpatentable over Chang, US Patent No. 5,723,125 ("Chang") in view of any one of Carozzi et al., U.S. Patent No. 5,686,600 ("Carozzi"), Dillon et al., US Patent No. 5,395,750 ("Dillon"), or Pastan et al., US Patent No. 5,990,296 ("Pastan").

Applicant respectfully disagrees on the ground that there is no required teaching, suggestion, or motivation to modify the disclosure in Chang as suggested by the Examiner in view of any one of Carozzi, Dillon, or Pastan.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See* MPEP 2143.01.

Claims 1, 2, 5, and 7-12 are drawn to a fusion protein comprising an interferon-alpha (IFN- α) joined at its C terminal through a peptide linker to an N terminal end of an immunoglobulin heavy chain having a hinge, C_H2 and C_H3 domain (Fc). The claimed peptide linker is chosen from the group (GGGGS)₂, (GGGGS)₃, and (GGGGS)₄.

Chang discloses a recombinant protein consisting of IFN- α and Fc, joined by a peptide linker comprising the amino acid sequence of GGS₂GGSGGGSGGGGS. As conceded by the Examiner on page 3 of the Office Action, Chang does not disclose any of the peptide linkers recited in pending claims. Linkers (GGGGS)₂, (GGGGS)₃, and (GGGGS)₄ linkers are disclosed in Carozzi, Dillon, and Pastan, respectively.

The Examiner stated that the linkers disclosed in Carozzi, Dillon, and Pastan are exchangeable equivalents to the linker disclosed in Chang because they all have the same art recognized function, similar structural characteristics, and are all used for the same purpose. *See* the Office Action at page 4.

Thus, according to the Examiner, the cited prior art linkers are allegedly freely interchangeable. Applicant respectfully disagrees and submits that the linkers taught in Carozzi, Dillon, and Pastan are all disclosed for a single specific and distinguishable purpose from that of Chang. Accordingly, it would not have been obvious to substitute any of the linkers taught in Carozzi, Dillon, and Pastan for the linker disclosed in Chang.

The linkers disclosed in each of in Carozzi, Dillon, and Pastan are used for a purpose different from the purpose of the linker in Chang. More particularly, the linkers taught in each of Carozzi, Dillon, and Pastan are used only to link V_H and V_L immunoglobulin polypeptides together to form single-chain antibodies (scFv). The (GGGGS)₂, (GGGGS)₃, and (GGGGS)₄ linkers disclosed by Carozzi, Dillon, and Pastan in each instance link one immunoglobulin polypeptide to another immunoglobulin polypeptide, to yield a scFv "antibody" that is functional

insofar as it binds specifically to a particular antigen. The combination of the two polypeptides in the scFv antibodies of the Carozzi, Dillon, and Pastan thus cooperate in maintaining their common antibody-like function.

A person skilled in the art would not have found sufficient teaching, motivation, or suggestion to substitute a linker disclosed in Carozzi, Dillon, or Pastan for the linker disclosed in Chang because the linker in Chang is used to join different polypeptides that are structurally and functionally unrelated to one another. In contrast to the scFv of Carozzi, Dillon, or Pastan, the chimeric fusion protein of Chang includes polypeptide components derived from functionally unrelated proteins (i.e., interferon-alpha and immunoglobulin Fc gamma chain). The requirements for a peptide linker joining these disparate components, with maintenance of their individual component functionalities, cannot be predicted from the disclosure of (GGGGS)₂, (GGGGS)₃, and (GGGGS)₄ linkers in Carozzi, Dillon, and Pastan, wherein the linkers are used to link V_H and V_L immunoglobulin polypeptides together to form single-chain antibodies (scFv).

In addition to there being no teaching, motivation, or suggestion to combine the references as suggested by the Examiner, there would be no reasonable expectation of success in arriving at the claimed invention. Due to the disparate nature of the components joined through the linker in the claimed invention, as compared to the related nature of the components joined through the linkers in the references by Carozzi, Dillon, and Pastan, at most it might have been *obvious to try* substituting a linker disclosed by Carozzi, Dillon, or Pastan for the linker disclosed in Chang. However the standard for obviousness is not simply *obvious to try*. Rather, there must be a specific teaching, motivation, or suggestion for making the combination, coupled with a reasonable expectation of success in arriving at the claimed invention.

Further in support of Applicant's argument it is respectfully pointed out that the (GGGGS)₃ linker in Carozzi is disclosed only for the purpose of linking V_H and V_L immunoglobulin polypeptides to each other to make a scFv, and not for linking a toxin moiety to the scFv.

Likewise, further in support of Applicant's argument it is respectfully pointed out that the (GGGGS)₄ linker in Pastan is disclosed only for the purpose of linking V_H and V_L

immunoglobulin polypeptides to each other to make a scFv, and not for linking a toxin moiety to the scFv.

In fact, Pastan makes a clear distinction between a (GGGGS)₄ *linker*, used to link V_H and V_L immunoglobulin polypeptides to each other to make a scFv, and a peptide *connector* (SGGPEGGS) used to connect the scFv to an effector (e.g., toxin) moiety. *See, e.g.*, Pastan, column 3, lines 28-35; column 4, lines 20-25; column 13, lines 35-39 and 45-47; and Figure 1B. A skilled person reading Pastan would likely have concluded that a (GGGGS)₄ *linker* can be used to join related V_H and V_L polypeptides, whereas a structurally distinct *connector* SGGPEGGS can be used to connect unrelated polypeptides. This teaching amounts to a teaching away from the substitution suggested by the Examiner.

In summary, Applicant respectfully submits that it would not have been obvious to substitute the linker of any of Carozzi, Dillon, or Pastan for the linker of Chang. Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 1, 2, 5, and 7-12 under 35 U.S.C. §103(a) as being unpatentable over Chang in view of any one of Carozzi, Dillon, or Pastan.

The Examiner also rejected claims 3, 4, 6, 11, 13, 18, 23, 28, 33, 40, 47, and 49 under 35 U.S.C. §103(a), all on grounds including the combination of Chang with at least one of Carozzi, Dillon, and Pastan. In view of the foregoing, Applicant respectfully submits that Chang cannot be combined with any of Carozzi, Dillon, or Pastan as suggested by the Examiner. Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw these additional rejections made under U.S.C. §103(a).

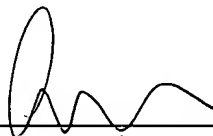
Conclusion

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Richard S. Blumberg, et al., Applicant(s)

By: _____


Alan W. Steele, M.D., Ph.D.
Reg. No. 45,128
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: S1383.70011US00
Date: 02/15/06
x02/15/06x